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Animal Models of Parkinson's Disease Progression

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose etiology is not understood. This disease occurs both sporadically and through inheritance of single genes, although the familial types are rare. Over the past decade or so, experimental and clinical data suggest that PD could be a multifactorial, neurodegenerative disease that involves strong interactions between the environment and genetic predisposition. Our understanding of the pathophysiology and motor deficits of the disease relies heavily on fundamental research on animal models and the last few years have seen an explosion of toxin-, inflammation- induced and genetically manipulated models. The insight gained from the use of such models has strongly advanced our understanding of the progression and stages of the disease. The models have also aided the development of novel therapies to improve symptomatic management, and they are critical for the development of neuroprotective strategies. This review critically evaluates these *in vivo* models and the roles they play in mimicking the progression of PD.

Keywords

substantia nigra; MPTP; 6-OHDA; rotenone; LPS; engrail; alpha-synuclein

Introduction

There are many theories on the etiology of Parkinson's disease (PD), but most agree that outside of the rare familial cases, this disorder involves interactions between genetic and environmental factors [64]. The primary neuropathological feature is the profound loss of dopaminergic (DA) nigrostriatal neurons. However, the neuropathology is not restricted to these neurons, for reductions in non-DA cells appear either before or subsequent to the substantia nigra (SN) loss [9,10,47]. Other prominent neuropathological features also emerge, including the accumulation of insoluble proteins, such as alpha-synuclein, in cytoplasmic inclusions called Lewy bodies in SN DA neurons and, in some cases, in non-dopaminergic neurons located elsewhere [1,49].

Investigators rely heavily on rodents to model the features of PD and provide insight into the mechanisms underlying the pathophysiology. However, there is controversy as to which model (s) best represent(s) the progressive nature of PD and whether a model can demonstrate the

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important distinction between “preclinical” and “clinical” disease states. Among the many models created over recent decades, the most widely used are those that employ toxins, such as 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, or paraquat, but demonstrating specific and progressive SN cell loss has been disappointing with some protocols. Nevertheless, several models are able to mimic one or more of the stages of PD, particularly if partial or graded lesions are induced.

We have known for decades that neuroinflammation is present in PD. There is an activated microglia response and increased microglial cytokine expression in the SN of PD patients [8, 54]. While the presence of reactive microglia in humans was initially thought to be a consequence of ongoing neuronal degeneration, we now believe that the microglia contribute to neurodegeneration [87]. Thus, inflammation-based models have been created. Lipopolysaccharide (LPS), an endotoxin derived from the cell wall of gram-negative bacteria, is a potent inducer of inflammation, a powerful activator of microglial cells, and can be used to model neuroinflammation in PD [133]. Progressive features have been demonstrated in some of these models.

Despite recent efforts to develop progressive toxin- or inflammation- based protocols, mouse or rat models created through the expression of genetic mutations may prove to be ideal for modeling disease progression. Indeed, progressive behavioral deterioration, increasing pathology with age, and alterations in motor function that manifest “subclinical” deficits have been demonstrated. The extent to which they reproduce many hallmarks of PD and the mechanisms at work in the sporadic forms of the disease vary greatly. Importantly, a few mouse lines exhibit non-progressive cell loss suggesting they do not reliably reproduce pathophysiological mechanisms of PD. This stresses the need to examine phenotypes at different ages.

In this review, we will discuss the ability of all these models to replicate the progression and extent of DA nigrostriatal loss found in PD and discuss the challenges and caveats of using them as models of preclinical or advanced disease states.

PD Models: Acute or Chronic Delivery of Neurotoxicants

Many different toxins are used to generate DA degeneration. Most are able to potently inhibit Complex I or enhance the production of reactive oxygen species (ROS) through their effect on mitochondria. Some specifically target the DA neurons through preferential uptake by transporters. An emphasis of recent research has been on the creation of models where exposure is chronic and damage occurs progressively to mimic human PD. As such, these models can be valuable to define early and late processes associated with neuronal degeneration and evaluate neuroprotective strategies during mid or late stage degeneration, which is when therapy in PD patients is initiated.

6-Hydroxydopamine—The neurotoxin, 6-OHDA, is structurally similar to dopamine and norepinephrine (NE) and has a high affinity for the plasma membrane transporters of these catecholamines [11]. Once inside the neurons, it is readily oxidized and produces hydrogen peroxide and paraquinone, both of which are highly toxic [103]. This toxin does not readily cross the blood-brain-barrier, but when administered directly in the brain, it specifically kills DA and NE neurons and their terminals [58,61]. Dismethylimipramine injected systemically before 6-OHDA protects NE neurons [11]. The degree of loss of DA neurons and their striatal terminals is dependent upon the location and dose of the toxin, as well as the survival time following the lesion (table 1). However, this toxin does not produce extra-nigral pathology or Lewy body-like inclusions [22,70].

6-hydroxydopamine is generally administered unilaterally to the SN, medial forebrain bundle (MFB) or striatum. Following delivery of 6-OHDA to the ventral midbrain, most concentrations destroy the SN DA cells within a few hours, and before the striatal terminals disappear [59], but when injected into the MFB, striatal terminals degenerate first, followed by DA cell death (table 1; [138]. Dopaminergic neurons in the ventral tegmental area (VTA) are virtually unaffected, which is similar to DA loss in PD [45]. Some of the earliest work with this toxin introduced it (25–200µg) intracisternally, which reduced brain DA levels by 70% and NE by 75% [11]. More recent investigations have used injection concentrations of 4–8µg/µl of the toxin in the SN or MFB. These latter doses rapidly reduce striatal DA levels by 90% percent and produce a nearly complete destruction of SN neurons and striatal tyrosine hydroxylase (TH)-immunoreactive terminals [45,122,138]. Interestingly, Stanic and colleagues [115] found that by 16 weeks after a partial SN lesion (less than 75%), the striatum is completely re-innervated by TH-immunoreactive fibers and the turning bias demonstrated by amphetamine normalizes (see below), indicating that only large lesions (greater than 75%) can permanently destroy the nigrostriatal pathway.

Among the motor tests used following 6-OHDA lesions, the ‘gold standard’ measures the magnitude of nigrostriatal loss and involves injecting the rat with apomorphine or amphetamine and counting the number of rotations [124]. The rotational tests are complex in that DA uptake inhibitors induce ipsilateral rotation, whereas DA agonists produce contralateral rotation [71]. Systemic injection of levodopa induces a robust contralateral rotation as does the receptor agonist, bromocriptine [99,124]. Because the 6-OHDA lesion is unilateral, animals show asymmetry in the cylinder and adjusting step motor tests [106]. Therefore, a large 6-OHDA lesion administered to the MFB produces an excellent model of late stage PD and has often been used to screen pharmacotherapies for symptomatic relief. Nevertheless, recent work has created 6-OHDA models of earlier stages of PD, using graded doses of toxin into the MFB (1, 2 or 4 µg/µl) and demonstrating abnormal locomotion, balance and posture [122]. Indeed, this model may be more effective in detecting motor abnormalities than other ‘bilateral’ toxin models, because the unilateral nature of the lesion forces a rat to shift its weight abnormally for locomotion and balance, thereby creating quantifiable deficits that are analogous to many seen in PD [60]. Moreover, PD often begins as a unilateral disorder progressing rapidly to bilateral symptoms, and the 6-OHDA model may recapitulate early motor signs, especially with a partial lesion.

When 6-OHDA is injected in the striatum, the loss of DA nigrostriatal pathway is more progressive than with injections in other locations, even though it is dose-dependent [97]. A large toxin dose (20µg) into the striatum reportedly destroys SN neurons slowly over weeks reaching a maximum cell loss by 16 weeks post-lesion [105]. Fleming and colleagues [30] gave ascending doses of 6-OHDA to the striatum through a unilateral indwelling cannula over 14 days. They were able to induce a 35% DA cell loss over this period and measure subtle, but significant, behavioral impairments suggesting that this method of delivery produces a progressive, perhaps preclinical, parkinsonism.

MPTP—The identification of MPTP, a synthetic heroin that kills DA neurons, led to it becoming among the most widely used toxins to mimic the hallmarks of PD [38]. This is because the toxic metabolite, MPP⁺ is a potent Complex I inhibitor in DA neurons and postmortem PD brains show Complex I damage [107]. Indeed, MPTP models have been most useful in studies of the molecular changes that underlie mitochondrial dysfunction [22,24].

In rodents, MPTP is delivered systemically, either i.p. or s.c., and with repeated injections. Rats are not susceptible to the toxin and MPTP potency varies among mouse strains [108]. Despite this, frequent injections and large doses, which are often required to produce significant DA depletion in mice [114], are associated with high mortality and may not produce large scale

cell death [48,95]. This toxin kills DA neurons rapidly at first (table 1), but if injected over time, continues to cause cell death [6].

Three MPTP protocols, with some variation, are widely used. The acute protocol generally involves 4 injections in one day at 2 h intervals. Subacute (or subchronic) administration is a once daily injection over 5–8 days [63,95]. One chronic regimen utilizes repeated treatments over 5 weeks and requires the co-administration of the adjuvant probenecid to retard the renal clearance of the toxic metabolites of MPTP [73,95]. For all these protocols, SN TH immunoreactive neurons disappear rapidly, but this loss may not reflect actual DA cell death if neurons are counted shortly after treatment, since MPTP down-regulates TH gene expression [134]. In the past few years, the introduction of unbiased stereology to count the TH-immunoreactive and the Nissl-stained neurons at least 7 days following any MPTP treatment has provided better estimates of DA cell loss for these models. Thus, a single injection of MPTP (30 mg/kg) induces a 20–30% loss of DA neurons [16], a modified acute paradigm of 2 injections/day over 2 days leads to a 35% loss [62], and 4 injections kill approximately 50% of the neurons [28]. The subacute regimen over 8 days produces a 24% loss of DA neurons [63]. In addition, there is stereological evidence that the subacute protocol leads to a strong recovery of the DA neurons over time [95], suggesting that the toxic insult with this regimen is insufficient for permanent destruction of the nigrostriatal pathway.

The chronic MPTP (plus probenecid) regimen produces a rapid but more progressive loss of SN DA neurons when compared to other MPTP protocols [95]. Within a week after this regimen, 50% of SN DA neurons have been lost and up to 70–80% have disappeared by 3 weeks post-treatment; The latter loss can still be demonstrated 6 months later [15,79,95]. Thus, this chronic regimen provides a short preclinical ‘window’ following toxin administration for the introduction of neuroprotective strategies (table 1). Accompanying DA loss is a reduction in concentrations of dopamine and TH-immunopositive fibers throughout the dorsal striatum, with a sparing of the nucleus accumbens. Small granular inclusions that contain alpha-synuclein, have been seen in DA SN neurons and limbic cortical cells between 3 and 24 weeks post-MPTP treatment [88,90].

Overall, the MPTP-treated mouse models are disappointing in that DA neurons die so rapidly and there is little progressive loss of the nigrostriatal DA pathway. Nevertheless, the pattern of DA terminal loss in the striatum replicates that of PD. Extra-nigral pathology has been demonstrated in reduced levels of monoamines other than dopamine [48,131] and the inclusions in cortical regions [90].

In terms of motor deficits, the different MPTP protocols have also been disappointing [89]. The Rotarod and open field locomotion tests have been widely employed but are only effective if they are administered shortly after treatment when the mice are still intoxicated by MPTP. Mice tested later sometimes show hyperactivity and no deficit on the Rotarod [89]. Nevertheless, more sensitive measures, such as gait analysis, or the pole or grid tests, have been able to detect DA loss as low as 50% [89]. Unfortunately, motor deficits do not correlate well with the degree of DA neuronal loss, striatal DA levels or the dose of MPTP [101].

Intraventricular MPP+—MPP+, the toxic metabolite of MPTP and a Complex I inhibitor, is an excellent substrate for the DA transporter, which explains its selectivity towards DA neurons. Systemic administration of MPP+ does not damage central DA neurons, because it does not readily cross the blood brain barrier due to its charge. However, its direct infusion into the brain effectively destroys much of the DA nigrostriatal pathway. A chronic rat model has been developed which involves the continuous delivery of MPP+ for 28 days via an osmotic minipump that delivers the toxicant to the left lateral cerebral ventricle [137,139]. This model is unilateral in order to avoid the moribund condition that arises with extensive bilateral loss

of DA neurons. This MPP⁺ treatment produces a dose-dependent, unilateral loss of striatal DA and TH on the side of the infusion. At low MPP⁺ doses (0.086 and 0.142 mg/kg/day), striatal DA is selectively reduced by 37% and 53%, respectively. While higher MPP⁺ doses (0.432 and 0.960 mg/kg/day) produce a greater DA loss (up to 90%), they also cause significant reductions in serotonin levels. At 0.142 mg/kg/day, there is a progressive loss of DA neurons. At 28 days after initiation of MPP⁺ treatment, SN DA cells are reduced by 35%; at 42 days, cell loss is further reduced to 65% in the ipsilateral side. On the contralateral side, DA cell number was similar in control animals and MPP⁺ animals evaluated at 28 days. At 42 days, in the contralateral side, there was a non-significant reduction in DA cell number (approximately 40%), findings, which indicate there may be delayed contralateral DA cell loss. These latter findings need to be further investigated because if a delay in contralateral DA loss occurs, this would better model the human condition in which unilateral motor deficits seen in the early stage of PD is replaced by bilateral deficits as the disease progresses. Also, at the latter time point, many surviving DA neurons are silver-stained, indicating ongoing degeneration. Other pathological findings include striatal and SN microglial activation and striatal inclusion bodies that immunoreact for alpha-synuclein and ubiquitin. One of the caveats is the apparent lack of inclusion bodies in the SN. However, upon ultrastructural examination of SN DA neurons, swollen and abnormal mitochondria with electron dense material are observed, reminiscent of defective mitochondria seen in other models and in cybrids from PD patients [37,88,121]. Whether SN inclusions develop with longer MPP⁺ exposures or survival times remains to be determined. No behavioral assessments were performed in these studies so we cannot correlate DA loss with motor deficits. While the model is technically challenging, it produces a reliable response with low variation, thus making it appealing for testing neuroprotective strategies during the phase of toxic insult and ongoing degeneration, the stage at which PD patients present with the disease.

Systemic Rotenone—Several epidemiological studies link pesticide exposure to PD [3, 25]. Rotenone, a naturally occurring pesticide used in the environment, is a Complex I mitochondrial inhibitor that has been used to generate the first chronic PD model: rats receive rotenone via osmotic minipumps for up to 5 weeks, i.v. or s.c. [5,53,110]. Rotenone is lipophilic, readily crosses cell membranes and easily penetrates the blood-brain-barrier. At 2–3 mg/kg/day, it produces a loss of striatal DA terminals followed by progressive degeneration of SN DA neurons. Notably, dying DA neurons contain cytoplasmic inclusions, which like Lewy bodies, are immunopositive for alpha-synuclein and ubiquitin. Other pathological features include elevations in oxidative damage, microgliosis and increased iron deposits. Behaviorally, the rats display prominent motor deficits [36]. The progressive nature of degeneration and presence of neuronal inclusions are advantages of the rotenone model over more acute administration of other toxins. However, even with identical experimental conditions, rotenone causes either selective damage to DA neurons or more widespread cell loss [5,110]. Thus, while the DA neurons may be most vulnerable to rotenone exposure, other unrelated populations can be damaged as well, and the high variability limits the utility of the model [36,140]. An i.p. route of administration may circumvent these problems. Alam and Schmidt [2], using chronic daily i.p. injections of rotenone (1.5–2.5 mg/kg/day for 60 days), observed reduced striatal DA content and TH immunoreactivity (immunoblots), and levodopa-responsive motor impairments. More recently, Greenamyre and colleagues have shown that rats treated i.p. (daily) with a 2.75–3.0 mg/kg dose, display other features of PD, including SN accumulation and aggregation of alpha-synuclein, microgliosis, iron accumulation, loss of enteric neurons and cardiac sympathetic denervation (Greenamyre, personal communication). These animals show less variability compared to the osmotic pump delivery paradigm, thus making this an attractive model for therapeutic testing in animals demonstrating early and late stages of parkinsonism (table 1).

Paraquat and Maneb—Other environmental toxins known to disrupt mitochondrial respiration and produce ROS have been systemically administered to produce mouse PD models (table 1; [96]). Among these is paraquat (PQ), a herbicide that crosses the blood-brain-barrier. Its neurotoxicity can be attributed to redox cycling and ROS formation. Within cells, PQ is transported into mitochondria by a carrier-mediated process [21], where it is reduced by Complex I forming a PQ radical capable oxidatively damaging the mitochondria. Thus, whereas MPP⁺ and rotenone directly inhibit Complex I function, PQ indirectly disrupts mitochondrial function via intra-mitochondrial ROS formation through Complex I interactions with PQ. Various investigators have demonstrated small but significant losses of SN DA neurons with PQ [12,36,69,85,93] and up-regulation and aggregation of alpha-synuclein [29, 83]. However, studies have yet to demonstrate progressive DA cell loss or motor deficits.

Maneb (manganese ethylenebisadithiocarbamate), a fungicide that inhibits glutamate transport and disrupts DA uptake and release [125,126], is generally co-administered with PQ subchronically to enhance toxicity. When combined with maneb (30mg/kg), PQ (10mg/kg) at 1–2 injections/week (3–6 weeks) destroys 50% of SN DA neurons in young mice [118]. In older mice (18 months of age), combined PQ/maneb treatment produces a more progressive DA cell loss, i.e. approximately 75% at 2 weeks and 88% at 12 weeks [117]. Studies in older rats have shown that they are very sensitive to the toxic effects of the combination PQ/maneb at the same doses used in younger mice [20,102]. Loss of DA neurons, motor impairment and microgliosis, which are found in both young and old rats, mimic different stages of clinical PD. However, a potential disadvantage of PQ/maneb treatment for older rats is systemic lung toxicity, which can be lethal [102].

PD models: acute and chronic inflammation

Neuroinflammation is mediated predominately by microglia, the resident immuno-competent and phagocytic cells within the CNS. Microglia, representing 5–20% of brain cells [7,26], exhibit, in their basal resting state, a ramified morphology that monitor the environment (reviewed in [133]). When activated, microglia undergo dramatic morphological changes, converting to an amoeboid state with enlarged cytoplasmic processes capable of phagocytosis. Activated cells also produce pro-inflammatory molecules such as chemokines, cytokines, nitric oxide and ROS used for clearing toxic debris [4,7,80]. The phagocytic activity is beneficial during neuronal development and in injury, as this process effectively removes cellular debris, but dysregulation or excessive activation, and ill-controlled ROS formation, can lead to an oxidative burden for neurons. Microglial-induced inflammation can be sustained and progressive [41,42,86]. The observation that microgliosis persists for years in humans and non-human primates following acute exposure to MPTP [72,86] indicates that the inflammatory response persists in the absence of continued exposure to the neurotoxicant, a feature important for understanding cell death in PD.

Acute Intracerebral LPS—Intracerebral injections of LPS (5 or 10 µg) into the cortex, hippocampus, striatum or SN of rats enhances the death of only SN DA neurons, possibly because microglial cell density in the SN is 4–5 times higher than in other regions [41,52, 65]. LPS is now well established as an effective initiator of DA neurodegeneration. Acute intranigral or supra-nigral LPS injections (2 µg) produce a rapid activation of microglia (within 24 h) and loss of striatal dopamine (by 4 days) accompanied by loss of SN DA neurons (by 21 days) [13,56]. While striatal dopamine is rapidly reduced, no further decline is seen up to 1 year, indicating a permanent lesion but a lack of progression [52]. Although acute LPS administration produces a rapid and intense microglial response, microglia morphology reverts to normal by 30 days, indicating a short-lived response and not a prolonged or progressive state of activation [56]. Rats exposed acutely to LPS rapidly lose TH-immunoreactive neurons in the SN and show unilateral behavioral deficits as evidenced by ipsiversive circling following

amphetamine administration [56]. Others have seen a more progressive loss of TH-immunoreactive neurons months after a single acute insult [98].

Chronic Intracerebral LPS—To overcome the short-lived microglial response and develop a more progressive PD model, LPS has been administered chronically to rats. LPS is infused via stereotactically implanted cannulae just above the SN using osmotic minipumps [41]. This exposure (5 ng/h) for 2 weeks produces a rapid microglial activation (within 3 days) and signs of oxidative stress that persists for at least 8 weeks. The activation precedes DA cell death, which is not significant until 6 weeks into the study, but is progressive (approximately 10%, 40% and 60% at 4, 6 and 10 weeks, respectively, after initiation of exposure). While this model is attractive in that it presents with progressive DA cell loss, it remains to be determined if motor symptoms accompany the cell loss, alpha-synuclein-positive inclusions in DA neurons form or extra-nigral pathology occurs. Moreover, the techniques pose a technical challenge.

Acute Systemic LPS—A recent report describes the effects of a single systemic injection of LPS (5 mg/kg i.p.) in a mouse. Brain TNF α mRNA and protein rapidly increase (by 7,336% and 653%, respectively) within 1 hr of administration and remain elevated for 10 months [98]. Likewise, microglia in several brain regions (hippocampus, cortex, SN) become activated within a few hours of administration. However, DA cell loss is delayed but is progressive. Significant SN DA cell loss is not observed until 7 months of age (23% loss) with further reductions seen at 10 months of age (47% loss). Unfortunately, striatal DA changes and alpha-synuclein aggregates or other SN cell inclusion bodies have yet to be investigated. Nonetheless, the studies indicate that a single exposure to a systemic inflammogen initiates a self-propagating response, which ultimately leads to the loss of SN DA neurons. Interestingly, progressive DA cell loss occurs in mice given a single systemic exposure to LPS, which contrasts with the lack of progressive DA neuron loss in rats provided with a single, acute, intra-nigral LPS infusion [13,52,56]. If findings in mice are confirmed, this model would be attractive, especially if inclusions form and behavior can be correlated with cell loss.

Intrauterine LPS—Carvey and colleagues have proposed that prenatal exposure to LPS not only creates a neuroinflammatory response but also disrupts the normal development of DA neurons. They studied the effects of prenatal LPS exposure on DA cell development and postnatal DA cell number in rats [77,78]. In utero exposure to LPS following a single injection of the endotoxin into gravid female rats causes a significant (29%) reduction in striatal DA and 27% and 22% reduction in SN DA cell number in offspring killed at 21 days or 18 months, respectively, findings that suggest that prenatal infections could potentially be a risk factor for PD [76,77]. Moreover, rotenone (1.25 mg/kg/day, 14 days, intrajugular) injected at 18 months of age to rats exposed prenatally to LPS, exerted a synergistic effect on DA cell loss. There was a significant reduction in SN DA neurons (39%), findings that suggest a pre-existing pro-inflammatory state can be a risk factor for environmental toxins [76]. Finally, the data demonstrate that exposures to different toxicants, separated by months or years, can synergize in their detrimental actions on DA neurons.

PD models: genetic manipulations

Three types of genetic models of PD have recently been developed. First, mouse models based on the deletion of genes important for the development or maintenance of DA neurons or their phenotype [55,109,113]. These mice exhibit DA cell loss at various times in their life, thus reproducing a cardinal feature of PD. However, they fail to reproduce the broad extra-nigral pathology and other pathological landmarks such as Lewy bodies. Furthermore, the relevance of these genetic mutations to PD is not fully established. Second, mouse or rat models based on expression or deletion of genes known to cause familial forms of PD [31]. Although these mutations are very rare, they point towards mechanisms that are most certainly related to PD

in humans. The relevance of these specific genes or mutations to sporadic PD, however, is only clearly established for alpha-synuclein, the gene in which the first PD-causing mutations were discovered [19]. Finally, a third class of genetic models is based on virally mediated expression of genes or mutations known to cause familial PD, usually in nigrostriatal DA neurons [123]. These models produce a more acute form of the disease than transgenic or knock out animals. Nevertheless, they are valuable because they often exhibit neuronal loss, a feature that has been elusive in genetically engineered mice expressing PD-causing mutations.

Genetically engineered mice: mutations leading to nigrostriatal DA cell loss—

Two models have achieved a progressive, post-natal loss of SN DA neurons:

1) *Pitx3* $-/-$ mice: These mice have a spontaneous mutation in the homeobox transcription factor *Pitx3* and were originally identified based on a small eye phenotype (and blindness) and named aphakia mice. After the role of *Pitx3* in DA development was identified, several groups discovered that these mice also lose nigrostriatal DA neurons early during post-natal development [55,91,111,127]. Aphakia mice show behavioral deficits that are reversed by levodopa [55,127]. Interestingly, mesolimbic DA neurons are resistant to *Pitx3* loss, similar to what is observed in PD. The relevance of this mutation to sporadic PD remained elusive until recent evidence that polymorphism in the *Pitx3* gene represents a risk factor for PD [39]. Nevertheless, the loss of DA neurons is the only PD feature reproduced in these mice; therefore, they may be useful to study survival factors for DA neurons or symptomatic treatments to counteract the consequences of striatal DA loss but can hardly be considered a model of the disease. Furthermore, they lack the characteristic progressive nature of sporadic PD, in which DA cell loss begins in adulthood.

2) *Engrailed knock-out (KO) mice:* *Engrail 1* is primarily expressed in mesencephalic DA neurons, whereas *engrail 2* is primarily expressed in cerebellum. To avoid compensation by one engrailed gene for the other, investigators generated *engrail 1* $+/-$ on a background of *engrail 2* $-/-$ (knocking out both forms of engrail is embryonic lethal) [109]. These mice show a progressive loss of nigrostriatal DA neurons but also cerebellar pathology, which limits their use in behavioral assays of nigrostriatal dysfunction. Another line that lacks one copy of *engrail 1* with preserved *engrail 2* shows more specific nigrostriatal DA cell loss without cerebellar pathology [113]. DA cell loss is progressive but it starts during late post-natal development, i.e. probably much earlier than in sporadic PD. These mice show behavioral deficits, including marked affective disorders, a frequent symptom of PD. The search for the relevance of engrailed mutations to PD remains ongoing.

Genetically engineered mice that express mutations of familial PD

Five mutations (alpha-synuclein, Parkin, PINK1, DJ1, and LRRK2) have been linked to familial PD [50,68]

1) *Alpha-synuclein overexpressing mice:* Single point mutations or gene multiplication of alpha-synuclein lead to familial forms of PD [74]. The latter indicates that increased levels of wild-type alpha-synuclein can cause PD. This establishes an important link with sporadic PD in which alpha-synuclein is not mutated but accumulates in Lewy bodies or neurites in a broad range of affected neurons, including but not limited to nigrostriatal DA neurons [47]. Many lines of mice expressing mutations in alpha-synuclein have been generated over the last decade [19]. They differ in the promoter used, which is critical in determining the relevance of the resulting line in modeling PD, and whether the transgene encodes wild-type or mutated alpha-synuclein. The TH promoter was used to reproduce the loss of catecholaminergic neurons found in PD. However, the restricted expression of the transgene does not mimic the broad alpha-synuclein pathology that characterizes the human disease. A different approach is to use a promoter that confers broad neuronal expression. The prion promoter has been particularly

successful in generating models of amyotrophic lateral sclerosis because it drives high levels of transgenes in motoneurons [43,75]. Accordingly, mice overexpressing alpha-synuclein under the prion promoter exhibit motor neuron pathology, which is different from PD. Therefore, these mice provide information on mechanisms of alpha-synuclein-driven cell death *in vivo*, but they would not be useful to identify the specific, cell autonomous mechanisms in PD. Furthermore, the motor deficits cannot be attributed to nigrostriatal dysfunction or other parkinsonian symptoms.

Other promoters used to over-express alpha-synuclein in mice include PDGFbeta and Thy-1 [17,84,100,128]. Both confer broad neural expression but the pattern of transgene expression varies [51]. The Thy-1 promoter drives higher levels of transgene expression in the SN pars compacta than the PDGFbeta promoter, thus better mimics the breadth of pathology observed in sporadic PD. Some lines using the Thy1 promoter display motor neuron pathology [128], but others do not, despite high levels of transgene expression [100]. The latter mice present progressive sensorimotor deficits starting as early as 2 months of age and worsening with age [33]. These deficits are detected with behavioral tests that are sensitive to nigrostriatal dysfunction [55], however they occur in the absence of DA cell loss, and accordingly, are not reversed by levodopa [34]. Therefore, these deficits do not correspond to the symptoms of parkinsonism observed in manifest PD but may represent early alterations in motor function that remain “subclinical” in patients. Indeed, these mice show olfactory and autonomic deficits similar to symptoms often observed before the onset of classical neurological symptoms in PD [32,35]. In addition, they exhibit proteinase K resistant alpha-synuclein aggregates, which increase in size and become widespread with age (unpublished observations, [29]). With standard housing, these mice do not lose DA neurons up to 18 months of age. Nevertheless, the progressive motor deficits indicative of neuronal dysfunction, non-motor symptoms, and progressive pathological anomalies that are strongly reminiscent of early stages of PD, provide the opportunity to analyze the role of alpha-synuclein accumulation in PD and to test novel therapeutic interventions to stop disease progression.

Few lines of alpha-synuclein transgenic mice show prominent loss of DA neurons, even though some show decreased striatal DA levels [84,120]. One line expresses a doubly mutated alpha-synuclein, combining two mutations that lead to PD in humans, under the TH promoter [119]. Interestingly, another mouse, expressing a truncated form of alpha-synuclein, shows profound loss of DA but, disappointingly, this phenotype is present in young animals and does not increase with age, thus failing to provide a useful model for PD progression [130].

In conclusion, among the many lines of mice developed to mimic the alpha-synuclein pathology observed in sporadic PD, only a few have emerged that provide useful information despite some shortcomings. We are still lacking a model that reproduces both the broad pathology of PD and a robust progressive loss of nigrostriatal DA neurons. The information provided by existing models now informs further efforts to generate such model.

2) Parkin, PINK1 and DJ1 KO mice: Many mutations in the gene encoding parkin cause a significant portion of early onset familial PD [132]. Most of these mutations likely cause a loss of function in parkin, a E3 ubiquitin ligase, probably leading to proteasomal dysfunction [50]. One parkin mutation (Q311X) however causes DA cell loss in *Drosophila* in a dominant manner and PD may occur in some patients heterozygous for parkin mutations [68,104].

Two separate lines of mice with exon3 mutations leading to a lack of protein expression show progressive sensorimotor dysfunction without DA cell loss [44,57], whereas one line with an exon7 deletion showed anomalies in paired-pulse inhibition and a non-progressive loss of NE neurons in the locus coeruleus [129]. Other lines showed no behavioral deficits [94], while others show non-motor deficits [140]. Exon3 deletion mice show evidence of oxidative stress

in proteomics studies [92]. In contrast to these lines, a more recent model shows not only progressive motor dysfunction but also DA cell loss at late ages [82]. These mice are transgenic for Q311X parkin, suggesting a dominant effect of this mutation.

In flies, both parkin and PINK1 mutations cause similar alterations in mitochondria [27]. This phenotype, however, is not observed in mice. Nevertheless, PINK1 KO mice show a decrease in evoked DA release in the striatum and deficits in corticostriatal plasticity that are reversed by DA agonists, suggesting they are secondary to the decrease in evoked DA release [67]. Indeed, multiple observations suggest that deficits in DA release machinery may be a primary mechanism eventually leading to the SN DA cell demise [116]. Examining the progression of these pathological phenotypes in mice should provide insights into the progression of DA neurodegeneration in humans.

DJ1 mutations cause decreased resistance to oxidative stress in cells, flies, and mice [27]. The association of these mutations with recessive forms of familial PD supports a long suspected role for oxidative stress in PD pathophysiology [46]. DJ1 KO mice, however, have little phenotype and do not develop DA cell loss [135], although some lines show an increased sensitivity to PQ [136].

3) LRRK2 mutations: A late onset familial PD can be caused by a mutation in the gene that encodes a leucine-rich repeat kinase 2 (LRRK2) [40]. It appears that cell toxicity of mutant LRRK2 is dependent on its kinase activity [112] and transgenic mouse models are currently being developed.

Viral delivery of genes related to PD-causing mutations

The lack of DA cell loss in most lines of genetically engineered mice expressing PD-causing mutations may be due to a number of factors, including the development of effective compensatory mechanisms. To overcome this problem, a number of models have been developed based on the acute delivery of virally expressed genes into the SN [123]. Because this requires stereotactic infusions, the rat has been most often used, although it is possible to adapt the technique to mice. After overexpression of alpha-synuclein either with a lentivirus or with an adeno-associated virus into the SN, rats develop a progressive loss of DA neurons and associated behavioral deficits [66,81]. Thus, these models are more effective in modeling the hallmark nigrostriatal degeneration of PD than most currently available genetically engineered mice. However, the local delivery of the genes does not reproduce the extra-nigral pathology and does not model the progressive development of this pathology throughout the nervous system.

Conclusions

Over the past 3 decades, there has been impressive advances in creating rodent models that demonstrate the progressive nature of PD. No model is perfect, but rodents can demonstrate many pathophysiological features of PD and their use has increased our understanding of the mechanisms underlying this neurodegenerative disorder [22] and opened doors to exploration of neuroprotective and neurorestorative strategies [23]. Rodents have drawbacks, such as their short life span or their quadrupedal locomotion and very different behavioral repertoire that preclude replication of some, typical PD motor deficits [14,89]. Nevertheless, toxin- and inflammation-induced models have been repeatedly refined and new transgenic mice developed, so that more 'progressive' rodent models are now available. For example, in terms of toxin models, the location (striatum rather than SN or MFB) for delivery of 6-OHDA seems to be quite important for slowing DA neuronal loss in the SN [105], and graded injections of this toxin can mimic preclinical or clinical stages [122]. Moreover, recently developed motor tests have demonstrated that the hemiparkinsonian rat can be an exceptional model of stepping,

postural and balance deficits of PD [60]. The MPTP models are clearly the most widely employed but are disappointing in replicating PD symptoms, due to the lack of progressive cell death or correlated motor symptoms of PD. Nevertheless, these models have been very useful for exploring the molecular basis for mitochondrial dysfunction [22]. Intracerebroventricular (ICV) administration of MPP+, systemic daily injection of rotenone, or chronic ICV LPS produce progressive DA neuron loss and, in many cases, behavioral deficits that replicate those seen in PD [2,41,137,139]. However, the latter approaches are all technically challenging.

Genetic models of PD have opened new perspectives for modeling and understanding the progression of PD but the advantages and disadvantages of each approach must be carefully considered. It is important to distinguish models that reproduce the progressive degeneration of nigrostriatal DA neurons from those that model disease progression in the whole organism. Genetic modeling of nigrostriatal degeneration complements toxin-induced neuronal loss by reproducing insults that are mechanistically linked to PD in humans. These models can provide useful information on stages of neurodegeneration, in particular on the interplay between protective and detrimental mechanisms, which are likely to contribute to the late onset of the disease and the effect of aging, a main risk factor for PD. For example: does neurodegeneration require age-related failure in autophagy or the accumulation of mitochondrial mutations? Are defense mechanisms, such as anti-apoptotic or anti-oxidant genes upregulated prior to the onset of cell death? Finally, the growing number of models exhibiting DA cell loss due to genetic mutation not yet known to be associated with PD, point towards new avenues of research for genetic risk factors for the disease.

Few models so far reproduce the progression of extra-nigral pathology that characterizes PD and is present both in the pre-manifest (before the classical motor symptoms appear) and in the manifest phase of the disease. KO mice expressing mutations that cause recessive forms of familial PD have progressive behavioral deficits but do not show alpha-synuclein pathology as in sporadic PD. The closest models to sporadic PD so far are based on the over-expression of alpha-synuclein under a broadly expressed neural promoter such as Thy-1. Although they have insoluble alpha-synuclein inclusions, they fail to exhibit true Lewy bodies. Nevertheless, these mice show progressive sensorimotor deficits as well as decreased olfaction and autonomic dysfunction [19]. Because these behavioral deficits occur in the absence of DA cell loss these mice provide a model of pre-manifest PD but the absence of DA cell loss limits their use as a model of manifest PD. They show a broad pattern of alpha-synuclein aggregates that is reminiscent but not identical to the progressive pathological stages of PD. Clearly, the use of the endogenous alpha-synuclein promoter would be necessary to more faithfully reproduce this pattern, but high levels of transgene expression may need the use of bacterial artificial chromosome (BAC) technology. Based on the information available from existing models, sophisticated genetic techniques such as specific expression or removal of the transgene in defined brain regions with Cre-Lox technologies, and the expression of highly pathological forms of alpha-synuclein, for example truncated and/or phosphorylated [18,75,120], should permit a more mechanistic analysis of PD pathology progression in a genetic animal model.

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Table 1

Features of PD recapitulated by systemic or central administration of toxins

toxin	time to greatest DA cell loss	striatal loss of dopamine	advantages	caveats
6-OHDA, into nigra or MFB	42 h	dose-dependent loss of DA innervation	1) full DA depletion of nigrostriatal pathway 2) mimics late-stage PD; graded lesions mimic earlier stages 3) test therapeutic strategies	1) not progressive 2) resembles axotomy 3) no inclusions 4) no extra-nigral pathology
6-OHDA, into striatum	16 wks	circumscribed loss of tyrosine hydroxylase immunoreactivity at injection site	1) progressive DA cell loss 2) produces incomplete lesions that mimic PD	1) strong striatal glial reaction 2) no inclusions 3) no extra-nigral pathology
MPTP, acute	24 h	dorsal striatum with sparing of nucleus accumbens	1) inhibits complex I activity 2) striatal TH loss mimics PD	1) not progressive 2) no inclusions
MPTP, subacute/subchronic	24 h	dorsal striatum with sparing of nucleus accumbens	1) inhibits complex I activity 2) test neuro-protective regimens	1) not progressive 2) recovery of some DA neurons over time 2) no inclusions
MPTP, (probenecid) chronic	3 weeks post-treatment	dorsal striatum with sparing of nucleus accumbens	1) inhibits complex I activity 2) alpha-synuclein inclusions in DA neurons 3) extra-nigral pathology	1) initial death of DA neurons is rapid 2) inclusions do not resemble Lewy bodies
Paraquat (PQ) and maneb	Within 7 days	little or no measurable change in striatal DA innervation	1) combination of PQ and maneb is more effective for DA depletion than PQ alone	1) inconsistent results on DA loss 2) no inclusions 3) no extra-nigral pathology
Rotenone, chronic pump	36 days or longer	dose-dependent loss of TH in dorsal striatum with sparing of nucleus accumbens	1) inhibits complex I activity 2) progressive DA cell loss 3) alpha-synuclein inclusions in DA neurons 4) i.p. administration shows extra-nigral pathology	1) large variations in animal sensitivity 2) variation in motor response
MPP+, chronic pump	42 days or longer	dorsal striatum with sparing of nucleus accumbens dose-dependent loss of DA innervation	1) inhibits complex I activity 2) progressive DA cell loss 3) damaged mitochondria	1) no inclusions in DA neurons 2) motor deficits have yet to be demonstrated

toxin	time to greatest DA cell loss	striatal loss of dopamine	advantages	caveats
LPS, acute into SN	21 days	dorsal striatum	1) activated microglia 2) rapid DA cell loss 3) permanent lesion	1) not progressive 2) no inclusions in DA neurons
LPS, chronic into SN	10 weeks	no data	1) chronic activation of microglia 2) progressive DA cell loss	1) no inclusions in DA neurons
LPS, acute systemic	7–10 months	no data	1) chronic activation of microglia 2) progressive DA cell loss	1) no inclusions in DA neurons